INFORMATION DISCLOSURE STATEMENTS

Applicants appreciate acknowledgement of the Information Disclosure Statements of August 21, 2001 and July 18, 2002. Four additional Information Disclosure Statements were filed in late April to early May, 2003. Applicants request acknowledgement of references contained in those four Information Disclosure Statements.

CLAIM OBJECTIONS

Claim 1 has been amended to delete recitation of non-elected proteins. Withdrawal of the objection is requested.

UTILITY OF CLAIMS 1-10 UNDER 35 USC §101

The Office Action lays out three utilities taught by the specification for the claimed antibodies:

- inhibit neoangiogenesis
- inhibit tumor growth
- isolate endothelial cells.

The specification also teaches the use of the claimed antibodies for diagnosis. See page 44, ¶ 105 ("Moreover, for diagnostic purposes, an intracellular protein may be an equally good target since cell lysates may be used rather than a whole cell assay."), as well as page 46, ¶ 110 ("Antibodies specific for such markers can be used to identify such cells, by contacting the antibodies with a population of cells containing some endothelial cells."), and page 47, ¶ 111 ("One can identify tumor endothelial cells for diagnostic purposes, testing cells suspected of

containing one or more TEMs.").

These teachings are sufficient on their face to fulfill the utility requirement under §101. Nonetheless, the Office Action faults the specification for not teaching the biological function or mechanism in a cell or animal. The initial burden in making rests on the PTO to make a *prima facie* case of lack of utility. "The PTO must have adequate support for its challenge to the credibility of applicant's statements as to utility. Only then does the burden shift to appellant [applicant] to provide rebuttal evidence." *In re Bundy,* 642 F.2d 430, 433 (C.C.P.A. 1981). A patentable utility is one that provides the art with subject matter which is useful, such as a pharmacological activity. "'Practical utility' is a shorthand way of attributing 'real-world' value to claimed subject matter. In other words, one skilled in the art can use a claimed discovery in a manner which provides some immediate benefit to the public." *Nelson v. Bowler,* 626 F.2d 853 (C.C.P.A. 1980). An applicant need not, however, disclose how an invention works. "If the disclosure is sufficient to enable the ordinary skilled worker in the art to practice the invention, it is immaterial whether the applicant understood or explained all the principles underlying it." *In re Chilowsky,* 229 F.2d 457 (C.C.P.A. 1956).

The biological function or mechanism is simply not required under the law. *Chilowsky, supra.* Applicants have taught real world, practical uses for the claimed subject matter. Diagnosis and therapy of cancer are well-established utilities both in the patent law and in the real world.

The Office Action faults the specification for not proving that the protein is expressed by endothelial cells. Applicants are not under any duty to prove this point. The Patent Office has provided no reason to believe that the protein is more likely not to be expressed than expressed.

This is the burden that the PTO must meet in order to shift the burden of proof regarding utility to the applicants. *Bundy, supra.*

The PTO has cited a number of isolated examples from the scientific literature where expression of a protein is regulated at the translational level and may not be correlated with its mRNA level. One of skill in the art would expect, however, that a highly expressed mRNA transcript would be translated at least to a detectable level. For highly expressed mRNA transcripts, the correlation with protein level is actually quite good. See Gygi et al., "Correlation between Protein and mRNA Abundance in Yeast," *Molecular and Cellular Biology, 19:*1720-1730, 1999; figure 5. As the highly abundant proteins are included, the correlation value climbs. ("If the 11 most abundant proteins were included, the correlation steadily increased to 0.94." Gygi et al., at page 1727, column lines 24-26.) See Figure 6.

Those of ordinary skill in the art expect differential SAGE data to reflect meaningful differences in protein expression. This is demonstrated by the work of Novatchkova and Eisenhaber, two independent scientists unrelated to the applicants. Novatchkova and Eisenhaber further analyzed the raw data underlying the subject application, which applicants made publicly available via the world wide web (domain name sagenet.org/angiogenesis.html). *BioEssays 23:* 1159-1175, 2001. They mapped gene sequences of differentially expressed genes to protein functions and mad functional groupings of the identified proteins. They found most of the identified TEM proteins to be extracellular (secreted or transmembrane). Most of the TEM proteins were also found to be engaged in ECM remodeling, cytoskeletal reorganization, and cell migration. See page 1165, column 2, third full paragraph. Novatchkova and Eisenhaber discuss and analyze the functions of the TEM proteins for at least four pages. Clearly, Novatchkova and Eisenhaber who are workers of at least ordinary skill in the field, considered the SAGE data of

differential transcript expression sufficiently reflective of actual protein function to use applicant's data for their analysis. Tellingly, Novatchkova and Eisenhaber discuss the issue of translational regulation.

> Changes at the level of translational regulation (fidelity of translation, stability of mRNA) as well as protein activation, modification and degradation processes can also contribute and my be decisive especially at early stages of angiogenic activation of endothelial cells before ECM remodeling and cell migration become their major task. Therefore, we think that expression profiling will contribute to the discovery of molecular mechanisms but other high throughput techniques, notably proteomics methods, as well as traditional phenomenon-focused biological approaches will remain indispensable.

Page 1173, column 1, last paragraph, emphasis added. While Novatchkova and Eisenhaber state that studies of translational regulation "can also contribute" to an understanding of the molecular processes of angiogenesis, they do not teach that the differential transcriptional results do not reflect the involved functions at the protein level. On the contrary, Novatchkova and Eisenhaber explicitly teach that expression profiling "will contribute to the discovery of molecular mechanisms" of angiogenesis. Thus those of skill in the art do not ignore the possibility that protein regulation may also occur during neoangiogenesis in addition to transcriptional regulation, nonetheless that does not cause them to doubt that differential transcriptional expression reflects critical protein functions. Novatchkova and Eisenhaber take the inventors' transcriptional data as very important and derive a host of protein functional conclusions from the data.

Cells do not simply induce a particular mRNA for storage purposes. Transcripts are induced for making the encoded proteins. It is only under particular conditions that translational control is used, for example, a change in nutritional status. Translational control is simply too

energetically expensive for a cell—it wastes the energy that the cell has already expended to make the mRNA.

The PTO has not met its burden of showing that applicants asserted real world utilities are not likely to work. The PTO merely speculates that they may not. But such speculation is legally insufficient to make a *prima facie* case of lack of utility.

The PTO also faults the application for not teaching a relationship between the protein and a specific disease. On the contrary, the applicants teach throughout the specification that TEM expression is associated with tumors, in particular colon tumors. ("One can identify tumor endothelial cells for diagnostic purposes, testing cells suspected of containing one or more TEMs." Specification at ¶ 111.) Withdrawal of this rejection is respectfully requested.

WRITTEN DESCRIPTION

The PTO mistakenly states that in order to comply with the Written Description Requirement of §112, first paragraph, applicants must provide "evidence that at the time of filing" they were in "possession of a molecule that comprises an antibody variable region." This is a misstatement of the law. Showing "possession" is one of the rationales for the requirement of an adequate written description. But showing physical possession is not the only way to provide an adequate written description, nor is it a showing of physical possession sufficient on its own. The requirement is for an adequate written description. Applicants provide a written description. The PTO has not pointed to any inadequacy in the description provided. In fact, the written description provides those of skill in the art with all that they need to practice the invention: the full amino acid sequence of TEM17 is taught (see SEQ ID NO:230); and expression of TEMs in recombinant hosts is taught (specification at ¶99). Because the art of

making antibodies is well-established, providing TEM 17 protein is sufficient to enable those of skill in the art to obtain a specific antibody for that protein.

Applicant draws the reader's attention to Example 16 of the Written Description Guidelines Training Materials (Appendix 1). This example closely corresponds to the facts of the present application. "The general knowledge in the art is such that antibodies are structurally well characterized... It is well known that antibodies can be made against virtually any protein." The example concludes, "one of skill in the art would have recognized that the spectrum of antibodies which bind to antigen X were implicitly disclosed as a result of the isolation of antigen X." Since the present application teaches the entire sequence of the extracellular domain of TEM 17 (antigen X) it has clearly disclosed the protein to those of skill in the art. Thus, it implicitly also provided antibodies that specifically bind to TEM 17. Withdrawal of the rejection is respectfully requested.

REJECTION OF CLAIMS 1-2 UNDER §102(b)

Claims 1 and 2 are rejected as anticipated by Jacobs WO 98/14576.

Jacobs is cited for two teachings:

1. a protein that has an epitope similar to SEQ ID NO: 230 (Jacobs SEQ ID NO: 38);
2. an antibody ("Compositions comprising an antibody which specifically reacts with such protein are also provided by the present invention." Page 19, lines 2-3.)

The PTO reasons that the antibody disclosed by Jacobs would be able to react with the TEM 17 protein.

Jacobs discloses about 20 ESTs and putative encoded proteins, without ascribing a specific function to any of them. Instead, the detailed description provides a catalog of possible

biological functions. Jacobs teaches that the proteins of the invention "are expected to exhibit one or more of the uses or biological activities identified below." The uses are:

- research uses
- nutritional uses
- cytokine and cell proliferation/differentiation activity
- immune stimulating or suppressing activity
- hematopoiesis regulating activity
- tissue growth activity
- tissue generation or regeneration activity
- activin/inhibin activity
- chemotactic/chemokinetic activity
- receptor/ligand activity
- anti-inflammatory activity
- cadherin/tumor invasion suppressor activity
- tumor inhibition activity
- other activities (a list of at least ten additional categories of activities)

Pages 36-54. Jacobs identifies none of these activities with the protein defined in his SEQ ID NO: 38 (the sequence with the closest homology to applicants' SEQ ID NO: 230). *Ipso facto*, Jacobs does not teach that SEQ ID NO: 38 is a cadherin. Yet Jacobs only teaches a utility for antibodies to proteins with cadherin activity. See page 52, line 24-31. Thus, Jacobs does not link the teaching of SEQ ID NO: 38 with the teaching of an antibody. The Federal Circuit has held that two statements in a single reference

> cannot be viewed in the abstract. Rather they must be considered in the context of the teaching of the entire reference. Further, a rejection cannot be predicated on the mere identification in [the reference] of individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.

In re Kotzab, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000). Jacobs provides no reason to combine the two disparate teachings. Jacobs, taken as a whole, does not describe the claimed subject matter.

Jacobs teaches that amino acid residues 1-100 of SEQ ID NO: 38 form a predicted leader/signal sequence and that the mature protein begins at amino acid residue 101. See page 26, lines 1-5: "Amino acids 1 to 100 are the predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 101". Leader/signal sequences are cleaved off of the preprotein upon protein maturation. Thus, even if, *arguendo,* Jacobs did teach antibodies to SEQ ID NO: 38, he would not have been understood to teach making an antibody to any of amino acid residues 1-100 of SEQ ID NO: 38 because they would not form part of his predicted, mature protein. The only remaining amino acid residues of SEQ ID NO: 38 are residues 101 to 108. This short sequence does not reside in the extracellular domain of TEM 17, however. The alignment of Jacobs' SEQ ID NO: 38 and applicant's SEQ ID NO: 230 is shown in Appendix 2. Jacobs' residue 1 aligns with residue 343 of SEQ ID NO: 230. Thus Jacobs' residues 101-108 align with SEQ ID NO: 230 residues 443-450. Applicant teaches that the extracellular domain extends only to residue 427: "TEM 17 (BSC-TEM 7) has a signal sequence which includes residues 1-18 and a transmembrane domain at residues 427-445. It is a cell surface marker with an extracellular region comprising residues 1-426." Specification at ¶ 72. Thus if Jacobs is construed as teaching the production of any antibodies to SEQ ID NO: 38, he

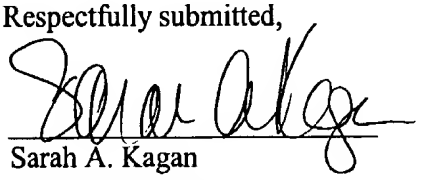
does not teach making antibodies which bind to the extracellular domain of TEM 17, as recited in applicant's claims 1 and 2.

Jacobs' teaching fails to anticipate the claimed subject matter because it is merely a list of hundreds of possibilities. Jacobs teaches that one of his many ESTs may encode a protein which has one of many functions. Jacobs further teaches that if one of the proteins does have one of the functions, then one might want to make antibodies to it. Jacobs fails, however, to provide a clear and unambiguous teaching of antibodies to the extracellular domain of TEM17. Moreover, even if Jacobs did teach making an antibody to his protein of SEQ ID NO: 38 in general, his other disclosures lead away from an antibody as claimed, *i.e.*, one which binds to the extracellular domain of TEM 17. Jacobs teaches that most of SEQ ID NO: 38 is not present in the mature protein. The remaining portion of SEQ ID NO: 38 is not within TEM 17's extracellular domain. Withdrawal is respectfully requested.

Withdrawal is respectfully requested.

Respectfully submitted,

Dated: January 13, 2004

By: 

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LISTING OF CLAIMS

1. (Currently Amended) An isolated molecule comprising an antibody variable region which specifically binds to an extracellular domain of ~~a~~ TEM ~~protein selected from the group consisting of: 1, 9,~~ 17~~, 19, and 44,~~ as shown in SEQ ID NO: ~~196, 212,~~ 230~~, 232, and 271, respectively~~.

2. (Currently Amended) The isolated molecule of claim 1 which is an ~~in tact~~ intact antibody molecule.

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3. (Original) The isolated molecule of claim 1 which is a single chain variable region (ScFv).

4. (Original) The isolated molecule of claim 1 which is a monoclonal antibody.

5. (Original) The isolated molecule of claim 1 which is a humanized antibody.

6. (Original) The isolated molecule of claim 1 which is a human antibody.

7. (Original) The isolated molecule of claim 1 which is bound to a cytotoxic moiety.

8. (Original) The isolated molecule of claim 1 which is bound to a therapeutic moiety.

9. (Original) The isolated molecule of claim 1 which is bound to a detectable moiety.

10. (Original) The isolated molecule of claim 1 which is bound to an anti-tumor agent.

18. (New) The isolated molecule of claim 4 which is bound to a cytotoxic moiety.

19. (New) The isolated molecule of claim 4 which is bound to a therapeutic moiety.

20. (New) The isolated molecule of claim 4 which is bound to a detectable moiety.

21. (New) The isolated molecule of claim 4 which is bound to an anti-tumor agent.

22. (New) The isolated molecule of claim 6 which is bound to a cytotoxic moiety.

23. (New) The isolated molecule of claim 6 which is bound to a therapeutic moiety.

24. (New) The isolated molecule of claim 6 which is bound to a detectable moiety.

25. (New) The isolated molecule of claim 6 which is bound to an anti-tumor agent.

26. (New) The isolated molecule of claim 1 wherein the antibody variable region specifically binds to residues 137-244 or 280-344 of TEM17.

27. (New) The isolated molecule of claim 2 wherein the antibody variable region specifically binds to residues 137-244 or 280-344 of TEM17.

28. (New) The isolated molecule of claim 3 wherein the antibody variable region specifically binds to residues 137-244 or 280-344 of TEM17.

29. (New) The isolated molecule of claim 4 wherein the antibody variable region specifically binds to residues 137-244 or 280-344 of TEM17.

30. (New) The isolated molecule of claim 5 wherein the antibody variable region specifically binds to residues 137-244 or 280-344 of TEM17.

31. (New) The isolated molecule of claim 6 wherein the antibody variable region specifically binds to residues 137-244 or 280-344 of TEM17.

32. (New) The isolated molecule of claim 1 wherein the antibody variable region specifically binds to residues 18-427 of TEM17.

33. (New) The isolated molecule of claim 2 wherein the antibody variable region specifically binds to residues 18-427 of TEM17.

34. (New) The isolated molecule of claim 3 wherein the antibody variable region specifically binds to residues 18-427 of TEM17.

35. (New) The isolated molecule of claim 4 wherein the antibody variable region specifically binds to residues 18-427 of TEM17.

36. (New) The isolated molecule of claim 5 wherein the antibody variable region specifically binds to residues 18-427 of TEM17.

37. (New) The isolated molecule of claim 6 wherein the antibody variable region specifically binds to residues 18-427 of TEM17.